

PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Duff et al.

Application No.: 09/247,874

Art Unit: 1632

Filed: February 10, 1999

Examiner:
Schnizer, R.

For: Therapeutics and Diagnostics Based)
on a Novel IL-1B Mutation)

Customer Number: 25181)



CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

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Robert King

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Commissioner for Patents
Washington, DC 20231

DECLARATION OF DR. FRANCESCO S. DI GIOVINE UNDER 37 CFR 1.132

Sir:

I, Francesco S. di Giovine, born on June 4, 1956, a University Senior Lecturer at the University of Sheffield, do hereby declare that:

1. I am one of the inventors of the above-identified application entitled "Therapeutics and Diagnostics Based on a Novel IL-1B Mutation".
2. I have an M.D. degree in Medicine and Surgery from the University of Florence (Italy), Faculty of Medicine, 1982, and a PhD degree in Molecular Immunology from the University of Edinburgh (UK), Faculty of Medicine. My curriculum vitae is attached hereto as Attachment A.

3. I am actively engaged in researching genetic predispositions to various inflammatory diseases.

4. As of the filing date of February 10, 1999, members of my laboratory had discovered and sequenced the IL-1B allele having a "C" rather than a "G" at the position corresponding to +6912 in Figure 1. This allele is also referred to as IL-1B (+6912) allele 2.

5. As described in the instant application (Example 1, pp. 36-37), a PCR product corresponding the 3' UTR of the IL-1B gene was amplified from human genomic DNA and sequenced. Sequencing data obtained in my laboratory is provided as Attachment B. Note that at position 199 in the sequencing chromatogram, there is an unambiguous reading of a "C". This position corresponds to the +6912 position of the published IL-1B sequence. This data was obtained prior to the filing date of February 10, 1999.

6. At the time that we performed these sequencing experiments, the human IL-1B sequence published by Clark et al. (Nucleic Acids Res. 14 (20), 7897-7914 (1986)) was regarded as the standard sequence for human IL-1B. This sequence is also deposited in Genbank under the accession number X04500. The Clark et al. sequence shows a "G" at position +6912, and when we discovered a sequence variation at this position, we named the "G" variation "allele 1" and the "C" variation "allele 2". Our measurements of allele frequency presented in the patent application (eg. Example 2, pp. 37-38) demonstrate that allele 1 is the more frequent allele and may therefore be considered the wild-type allele.

7. As set forth in the present application, the IL-1B (+6912) allele 2 is associated with an increased frequency of a variety of disorders. This association is demonstrated statistically and does not depend upon any mechanism by which the IL-1B (+6912) allele 2 might cause any of a variety of disorders. An allele may be considered associated with a disorder if it is tightly linked (or in "linkage disequilibrium") with an allele that is itself known to be associated with a disorder (for a discussion of these issues, see WO 98/54359, cited by the Examiner, pp.1 - 2). For example, IL-1B (+3954) allele 2 is associated with periodontal disease, psoriasis, insulin-dependent diabetes and many other disorders (eg. see WO 98/54359, Duff et al., cited by Examiner). Therefore, the detection of IL-1B (+3954) allele 2 in a subject indicates that the subject is predisposed to each of those disorders. The instant application teaches (see for example, pp. 44-46 and Table 3) that subjects carrying the IL-1B (+3954) allele 2 are greater than 99% likely to carry IL-1B (+6912) allele 2. Therefore detecting the IL-1B (+6912) genotype will be at least as predictive as detecting the IL-1B (+3954) allele 2. Accordingly, whether or not the overexpression of IL-1B caused by the IL-1B (+6912) allele 2 plays any role in causing disease, detection of the IL-1B (+6912) allele 2 is useful for, among other things, the identification of subjects that are predisposed to develop a variety of disorders.

8. In conclusion, at the time of filing I was in possession of a novel IL-1B sequence with a "C" at position +6912 (the position is as calculated from the transcription start site). This allele is termed the IL-1B (+6912) allele 2 and is substantially less common than the IL-1B (+6912) allele 1 known in the prior art. The IL-1B (+6912) allele 2 is associated with an increased likelihood of developing a variety of disorders.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 Title 18 of the United States Code, and that such wilful false statements may jeopardize the validity of the application of any patent issuing thereon.

27/2/01
Date

Francesco S. di Giovine
Francesco S. di Giovine, MD, PhD

ATTACHMENT A



Application No.: 09/247,874

Inventor: Duff, et al.

Examiner: R. Schnizer



University of Sheffield**CURRICULUM VITAE**

Francesco S. di Giovine, MD, PhD

**Scope and aims**

The main scope of my research is the genetics of inflammation. In the last few years I have worked in population genetics. A large resource of DNA from patient populations is being built in the Division of MGM, and it is available to answer specific questions arising from my current work.

Summary

- Since medical school (University of Florence), I have been interested in the mechanisms of inflammation, and wrote my MD thesis on metalloproteinases in rheumatic diseases.
- During my PhD at the University of Edinburgh I worked on cytokines in Rheumatoid Arthritis (TNF and IL-1) in the group of Prof. G.W. Duff. I confirmed that urate crystals induced IL-1 and TNF (articles n. 5 and 19) supporting a role for these cytokines in gout. Our group first showed that circulating IL-1 (art. 13) and sIL-2r (art. 12) correlated with disease activity in R.A.
- In 1986 we first reported the presence of TNF alpha in joint effusions from patients with R.A. (BSR A.G.M., December 1986; abstr. n. 9 and art. n. 7). In the subsequent years anti-TNF therapies have been developed and licensed world-wide. The importance of TNF in the rheumatoid process is now fully acknowledged and described in medical textbooks.
- In the late 1980's our group began exploring the genetic role of cytokines and started the mapping of DNA polymorphisms in cytokine genes. My work in this area led to the first reported promoter polymorphism in a cytokine, i.e. IL-1B (-511) (abstr. n. 57 and art n. 23). Since then we have reported a number of single nucleotide polymorphisms, including TNFA(-308), IL-1RN (+2018). Our work pioneered the field of cytokine genetics, and established important genetic associations between IL-1 and TNF gene variants and several important inflammatory diseases.
- Of particular interests, we have reported association and/or linkage between the IL-1 gene cluster and periodontal disease, cardiovascular disease, asthma, and R.A. I am consequently a co-inventor of several international patent applications, based on clinical use of the predictive value of these haplotypes.

1- Personal details

1.1 **SURNAME:** di Giovine
 1.2 **FORENAMES:** Francesco Saverio
 1.3 **DATE OF BIRTH:** 04.06.56 (Florence, Italy).
 1.4 **DEPARTMENT:** Division of Molecular and Genetic Medicine
 1.5 **EDUCATION:**
 Oct. 1970 - July 1975 "Classic Studies High School -Liceo Statale Galileo", Florence (Italy).
 Oct 1975 - July 1982 MD degree, University of Florence, Facolta' di Medicina e Chirurgia
 Oct 1982 - July 1984 Internal Medicine Course, University of Florence.
 July 1984 - Dec 1988 Ph.D. Course, Department of Medicine, University of Edinburgh, UK.

1.6 AWARDS AND SCHOLARSHIPS

1964-79 Twelve competitive Italian Ministry of Finance scholarships.
 1969,1970 Two top student awards "Cassa di Risparmio".
 1982 Magna cum laude from University of Florence Medical School
 1982 One of ten places (from 140 applicants) for specialist training in Internal Medicine

1.7 DEGREES:

July 1982 MD, University of Florence. Graduation: 24/7/82. Score: 110 cum laude/110.
 Proficiency exams score: 28.76/30. Thesis: "Human lung elastin resistance to proteolytic cleavage by elastase: correlations with age, sex, and the presence of emphysema".
 Supervisor: Prof. L. Andreotti.
 Dec 1988 PhD, University of Edinburgh (UK). Thesis: "The production of Interleukin 1 and Tumour Necrosis Factor by human monocytes, and evidence for a role in human arthritis".
 Supervisor: Dr. GW Duff.

1.8 CLINICAL TRAINING (University of Florence):

Feb 79 - Dec 81 Internal Medicine (Prof. Arcangeli), Rheumatology (Prof. Andreotti), Respiratory Medicine (Prof. Ricca). University Dept. of Internal Medicine, 3rd Division.
 Jan 82 - Feb 82 University Dept of Obstetrics and Gynecology (Prof. Gasparri).
 Mar 82 - Apr 82 University Dept of Dermatology (Prof. Giannotti).
 May 82 - Jun 82 Dept of Radiology and Radiotherapy (Prof. de Dominicis).
 Aug 82 - Oct 82 Dept of General Surgery (Prof. Loddi)
 Nov 82 - Jun 84 Intern, University Dept of Internal Medicine, 3rd Division (Prof Andreotti, Rheumatology; Prof. Arcangeli, Respiratory Medicine).

1.9 CLINICAL REGISTRATION:

Sept 1982 Professional National Exam (For Registration as a Medical Practitioner, "Esame di Stato"). Score: 82/90
 Oct. 1982 Joined the National Register of Medical Practitioners, Florence (Italy) n. 05513 – Reg. 7254 (Florence)

1.10 MEMBERSHIP OF LEARNED SOCIETIES

1. British Society for Immunology
2. British Society for Rheumatology

3. British Society for Histocompatibility and Immunogenetics
4. International Cytokine Society
5. Italian Society for Rheumatology

1.11 EMPLOYMENT:

University of Edinburgh

Jan 1985 Doctoral Research Fellow
 Dec 1988 Postdoctoral Research Fellow.
 Department of Medicine (WGH), Molecular Immunology Group.

University of Sheffield

Sept. 1990 Non-clinical Lecturer
 March 1994 Non-clinical Senior Lecturer, Section of Molecular Medicine.

2- Research2.1 RESEARCH AREAS

- Cytokines in the pathogenesis of autoimmune and inflammatory disorders
- Cytokine genetics and gene regulation.

2.2 RESEARCH GRANTS AND CONTRACTS2.2.1 *Grants held (1989-2000)*

1989	Oliver Bird Fund for Research into Rheumatism, Nuffield Foundation "Identification of retroviral sequences integrated in the genome of RA patients". One year. GW Duff, FdG	£ 8,914.
1990	Oliver Bird Fund for Research into Rheumatism, Nuffield Foundation. Modulation of cytokine gene expression in R.A. using antisense phosphorothioate oligonucleotides". Two years. GW Duff, FdG , JA Symons	£20,604.
1991	The Special Trustees of the Former United Sheffield Hospitals "The regulation of cell proliferation at the advancing, active edge of psoriatic plaques". One year, MJ Cork, A. Messenger, FdG , GW Duff	£ 23,000.
1991	The University of Sheffield Research Fund, "For a study of the molecular biology of cytokine production in psoriasis". One year, MJ Cork, A. Messenger, FdG , JA Symons, GW Duff	£ 12,000.
1992	The Psoriasis Association. "The induction pathway of cytokine gene expression as psoriatic lesions develop". One year, MJ Cork, FdG , , GW Duff	£ 12,633.
1992	National Association for Colitis and Crohn's disease. "Development of a DNA bank for genetic studies in inflammatory bowel diseases". One year. J. Mansfield, FdG , A. Blakemore, GW Duff	£ 24,336.
1993	The Special Trustees of the Former United Sheffield Hospitals. "The molecular genetics of inflammatory diseases". M. Cork, J. Mansfield, R.M. Wilson, D. Gleeson, A. Blakemore, FdG, GW Duff One year	£ 23,800
1993 7,970.	University of Sheffield Research Fund. "Urothelial cell culture for the study of bladder pathology and therapeutics in vitro." One year G. Singh, FdG , A Thomas, GW Duff	£
1994	Arthritis and Rheumatism Council. Equipment grant: "In support of a molecular imager, PC system, printer and maintenance.". One year MJ Nicklin, FdG , GW Duff	£ 25,000.

1998 Interleukin Genetics Inc (Formerly Medical Science Systems, Inc.)
 Renewal of Post-doctoral fellowship for Dr J Sorrell and consumables
 for confirmatory genetic studies in periodontal disease.
 Two years, FdG, GW Duff £ 60,000.

1998 Interleukin Genetics Inc (Formerly Medical Science Systems, Inc.)
 Technical salary and consumables for research and development of
 genetic prediction of inflammatory diseases.
 Two years, FdG, GW Duff £ 50,000.

2.2.2 Active grants

1999 British Digestive Foundation, Fellowship to Dr Martyn Carter
 Two years (FdG sponsor), £ 76,000.

1999 The Special Trustees of the Former United Sheffield Hospitals.
 "Cytokine polymorphisms as risk factor for the development of Deep Vein Thrombosis"
 One year, M Makris, FdG, A Cox £ 32,319.

1999 Crohn's in Childhood Research Association.
 "The Genetics of Ulcerative Colitis"
 One year, M Carter, FdG, GW Duff, A Lobo. £ 19,000.

2000 Arthritis Research Campaign.
 "Academic Secretary Grant for The Division of Molecular and Genetic Medicine,
 University of Sheffield."
 Three years, AG Wilson, A Adebajo, M Akil, FdG, GW Duff £ 51,591.

2.3 PUBLICATIONS (see details in section 6)

- Refereed journal articles: 55 in print, 2 in press, 6 submitted.
- Book chapters: 9 in print.
- Non-refereed, invited papers 5 in print.
- Refereed, published abstracts: 126 in print.

3- Teaching

3.1 CURRENT TEACHING (2000)

Nov. 2000 One lecture, MSc in Genetics, Faculty of Medicine.

3.2 PREVIOUS TEACHING

University of Edinburgh:

1985 - 1986 Supervision of two phase III medical students (2 months research projects)
 1986 - 1990 Supervisor, elective and honours students in their research projects (Two from Faculty
 of Medicine, one from Zoology and one from Biological Sciences).
 1988 - 1990 "Immunological investigations" course to IV year medical students (Rheumatology, Dept
 of Medicine). One lecture a week for eight weeks.
 1989 University of Edinburgh/Heriot-Watt University Biotechnology Course "Biological and
 Clinical application of Cytokines"
 1989 - 1990 Intercalated Honours course in Pharmacology ("Receptors in the immune system"). Two
 lectures.

Intercalated Honours course in Immunology ("Cytokines and immune activation"). Two lectures.
Tutor, phase I medical students ("Molecular Medicine, Facts and Fantasies") twelve students for 9 weeks (one morning a week)

University of Sheffield

1991 - 1992	Faculty of Medicine and Dentistry. Supervision of one B.Med.Sci student (J Hackney), graduated in May 1992 with First class honours degree.
1992 - 1993	Supervision of three PhD students (AG Wilson, J Tarlow).
1993 - 1994	Faculty of Science. Pharmacology BSc: Pharm 206- "DNA and Cancer Chemotherapy" course.
1993 - 1994 mechanisms	Faculty of Medicine and Dentistry, Clinical Phase 1 Integrated blocks: -Osteoarticular module. "How inflammation is generated". One lecture.
1994-1996	Faculty of Science, BSc Pharmacology, Pharmacology 206 module : "Molecular of cancer and chemotherapy" One lecture.
PhD	Faculty of Medicine and Dentistry, Clinical Phase 1 Integrated blocks: . Haematology Immunology/Genetics/Oncology module. Three lectures.
1996 -1997	Faculty of Science, BSc Pharmacology, 206 module : "Molecular mechanisms of cancer and chemotherapy". Two lectures.. Faculty of Law, MA in Biotechnological Law and Ethics. Two lectures.
1998-2000	Sheffield Hallam University, academic adviser for BSc student (J.Timms). Post-graduate co-ordinator and tutor , Section of Molecular Medicine. Supervisor of one student: A. Chaudhary (graduated in 1998)
	Supervisor of one MPhil student: E. Oppenheim. Thesis submitted and course finished in 1996.
	Faculty of Medicine and Dentistry, Clinical Phase 1 Integrated blocks: . -Haematology/Immunology/Genetics/Oncology module. Two lectures.
	Faculty of Law, MA in Biotechnological Law and Ethics. One lecture.
	Post-graduate co-ordinator and tutor , Section of Molecular Medicine.
	PhD Supervisor CC Campbell (graduated in 1999)
	- Undergraduates: Faculty of Dentistry, Mechanisms of Disease Course. One lecture.
	- Postgraduates: Supervisor of two MD students (M. Akil and M. Carter).

4- Administration

Present Administrative activities (1996-2000)

While the new Divisional organisation was in the making (eight months between 1996-1997), I was Acting Head of Molecular Medicine, a Section of approximately 25 staff.

From November 1997 to October 1999 I was convenor of the Resource Management Task Group, a group that monitors resource utilisation according to needs and opportunities and reports to the Divisional Committee; and a member of the Finance Task Group, which plays a key role in the administration of the Division.

In the commercial partnership between Interleukin Genetics and the University of Sheffield I had the role of project liaison with counterparts in ILGN, and was closely involved in the set-up of an R+D laboratory within Molecular Medicine, and supervised auditing and research record-keeping.

All of these administrative activities were abandoned in the summer of 1999, when I started a Sabbatical Year in the Laboratory of Prof PW Ingham, Developmental Genetics Programme.

Previous Administrative activities

Between September 1990 and October 1991 I had a central role in planning the laboratory space in the Department of Medicine, Floor M, (R.H.H). I supervised the design of the facilities, the use of space and the levels of containment for genetic manipulation and mammalian tissue culture. I personally liaised with Prof G. Duff and Prof I. Peake for the choice of equipment for the section of Molecular Medicine and the communal facilities (with the Section of Molecular Genetics), negotiating prices for the equipment bought and their service contracts. Our laboratories have been visited and used as models in the course of refurbishment of other facilities in the Medical school of this University.

Between 1992 and 1993 I organised the Oligonucleotide Service of this Department (including optimisation of stock, monitoring of efficiency and weekly financial routines. This service produced oligonucleotides with excellent value for money and a rapid turnaround of orders. By the end of 1993 we had orders for about £ 25,000, i.e. approx 600 oligonucleotides. In 1994 I was involved in the planning of the laboratory for the new DNA-sequencing facility of this Department and I monitored its financial side for the first year. In 1994 both services passed in the hands of Dr J Sayers, then newly appointed Lecturer to manage this facilities. I have been the Sectional Seqnet/Daresbury and MRC/Human Genome database representative, and I have overseen the initial computer installations in our Section.

Member of the Departmental Library and Computing committees, which were formed to decide departmental policy regarding academic use of the Library, deciding subscriptions and book purchase and computing policies. We introduced a computer-based bibliography service for the Department.

In June 1996 I have been invited to the University of Sheffield Socrates- Italy and Greece country group, a group formed to establish Socrates links with foreign Universities.

I have been on the panel for the appointment of senior technical staff, postdoctoral research fellows and academic members of Faculty.

5- Professional activities

- Head of PE-ABI European reference center, FRET-mediated allelic discrimination (1997-1999)
- Co-inventor on five international patents in the field of genetic diagnostics, University of Sheffield.
- Editorial board member, "International Journal of Immunopathology and Pharmacology" (1987-)
- Editorial board member, "Genes and Immunity" (1999-)
- Editorial Board Member, "Giornale Italiano delle Malattie Reumatiche" (1999-)
- Ad hoc reviewer for "Arthritis and Rheumatism", "British Journal of Rheumatology", "Cytokine", "Clinical and Experimental Rheumatology", "Journal of Rheumatology", "Scand. J. Immunol", "British Journal of Haematology", "European Cytokine Network", "Clinical and Experimental Immunology", "Gut", "Disease Markers".
- Consultant to NIH grant, U. of Virginia Dept. Gastroenterology. "Genetic analysis of Ulcerative Colitis" (1995-1997)
- Grants reviewed for the Arthritis and Rheumatism Council, The Wellcome Trust, Trent Regional Health Authority, North Western Regional Health Authority.
- External PhD examiner, Queen's University, Belfast, May 1993.
- Visiting Professor, University of Southern California, Los Angeles, March 1994.
- Since 1987, approximately 75 talks as invited speaker in UK, European and US Venues.
- Internal PhD examiners, University of Sheffield - several times in the last three years.

6- Publications

6.1 REFEREED ORIGINAL ARTICLES

- 1 Andreotti L, Bussotti A, Cammelli D, Sampognaro S, Cai A, Tanini A, **di Giovine F**, -J- Starrantino G, Varcasia G (1983). "Alterazioni del collagene nell'alcaptonuria" **REUMATISMO**, 35(3): 227-232.
- 2 Andreotti L, Cammelli D, Sampognaro S, Allori A, Baldoni D, Bussotti A, Cortini P, -J- **di Giovine F**, Starrantino G (1985) "Biochemical analysis of dermal connective tissue in subjects affected by primary uncomplicated varicose veins" **ANGIOLOGY**, 36(5): 265-270
- 3 Andreotti L, Bussotti A, Cammelli D, **di Giovine F**, Sampognaro S, Starrantino S, -J- Varcasia G, Arcangeli P (1985). "Aortic connective tissue in ageing - a biochemical study" **ANGIOLOGY**, 37 (12): 872-879
- 4 Andreotti L, Bussotti A, Cammelli D, **di Giovine F**, Starrantino G, Varcasia G, Arcangeli P -J- (1986). "Aortic connective tissue in atherosclerotic aorta - a biochemical study" **ANGIOLOGY**, 38 (10): 735-743
- 5 **di Giovine FS**, Malawista SE, Nuki G, Duff GW (1987) "Interleukin 1 (IL-1) as a mediator of crystal arthritis. Stimulation of T cell and synovial fibroblast mitogenesis by urate crystal-induced IL-1" **J IMMUNOL**, 138 (10): 3213-3218
- 6 Saxne T, **di Giovine FS**, Heinegaard D, Duff GW, Wolheim FA (1988). "Synovial fluid concentrations of interleukin 1 beta and proteoglycans are inversely related" **J AUTOIMMUNITY**, 1: 373-380
- 7 **di Giovine FS**, Nuki G, Duff GW (1988)
-P- "Tumor necrosis factor in synovial exudates" **ANN RHEUM DIS**, 47: 768-772
- 8 **di Giovine FS**, Meager A, Leung H, Duff GW (1988). "Immunoreactive tumour necrosis factor alpha and biological inhibitor(s) in synovial fluids from rheumatic patients" **INT J IMMUNOPATH PHARMACOL**, 1: 17-26
- 9 Cammelli D, Farnoli R, Salvadori A, **di Giovine FS**, Andreotti L (1988)
-J- "Sternocostoclavicular hyperostosis: report of a case"

REUMATISMO, 40: 75-85

- 10 Duff GW, Dickens E, Wood NC, Symons, JA, Poole S, and **di Giovine FS** (1988)
-J- "Immunoassay, bioassay and in situ hybridization of monokines in human arthritis"
In: "**Monokines and other non-lymphocytic cytokines**", pp 387-392. Eds Powanda
MC, Oppenheim JJ, Kluger M, Dinarello CA. Alan R Liss Inc (New York)
- 11 Manson JC, Symons JA, **di Giovine FS**, Poole S, Duff GW (1988)
-J- "Autoregulation of IL1 protein production" pp 109-112
In: "**Monokines and other non-lymphocytic cytokines**". Eds Powanda MC,
Oppenheim JJ, Kluger M, Dinarello C. Alan R Liss Inc publisher, New York
- 12 Symons JA, Wood NC, **di Giovine FS**, Duff GW (1988) "Soluble interleukin 2 receptor
-J- in rheumatoid arthritis: correlation with disease activity and interleukin 2 inhibition"
J IMMUNOL 141: 2612-2618
- 13 Eastgate JA, Symons JA, Wood NC, Grinlinton FM, **di Giovine FS**, Duff GW
(1988)"Correlation of plasma interleukin 1 with disease activity in rheumatoid arthritis"
LANCET, i, 706-709.
- 14 Manson JC, Symons JA, **di Giovine FS**, Poole S, Duff GW (1989)
-J- "Autoregulation of interleukin 1 production"
EUR J IMMUNOL 19:261-265
- 15 Symons JA, McDowell TL, **di Giovine FS**, Wood NC, Capper SJ, Duff GW (1989)
-J- "Interleukin 1 in rheumatoid arthritis: potentiation of immune responses within the joint"
LYMPHOKINE RES 8:365-372
- 16 **di Giovine FS**, Poole S, Situnayake RD, Wadhwa M, Duff GW (1990)
-P- "Absence of correlations between indices of systemic inflammation and
synovial fluid Interleukin 1 (alpha and beta) in rheumatic diseases"
RHEUMATOL INT, 9:259-264
- 17 **di Giovine FS**, Duff GW (1990) "Interleukin 1: the first interleukin" (**Review**)
-P- **IMMUNOL TODAY**, 11:13-20
- 18 Symons JA, Wood NC, **di Giovine FS**, Duff GW (1990)
-J- "Soluble CD8 in serum and synovial fluid from patients with rheumatic disease"
CLIN EXP IMM, 80: 354-359
- 19 **di Giovine, FS**, Malawista, SE, Thornton, E, Duff, GW (1991) "Urate crystals stimulate -
P- production of Tumour Necrosis Factor Alpha from human blood monocytes and synovial
cells Cytokine mRNA and Protein kinetics, and cellular distribution"
J. CLIN. INV., 87: 1375-1381
- 20 **di Giovine FS**, Symons JA, Duff GW (1991) "Kinetics of Interleukin 1 beta mRNA and -
P- protein accumulation in human mononuclear cells"
IMMUNOL. LETT., 29: 211-218
- 21 Ralston S, **di Giovine FS**, Gallacher SG, Boyle IT, Duff GW (1991)
-J- "Failure to detect paramyxovirus sequences in Paget's disease of bone using
the Polymerase chain reaction" **J. BONE. MIN. RES.** 6, 1243-1248
- 22- **di Giovine, FS** (1991) "Cytokines in arthritis" (**Review**)
-P- **REUMATISMO**, 42 (3): 203-215
- 23 **di Giovine, FS**, Takhsh, E, Blakemore, AIF, Duff GW (1992)
-P- "Single base polymorphism at -511 in the human Interleukin 1 beta gene"
HUMAN MOL. GENETICS, 1, 450.
- 24- Wilson AG, **di Giovine, FS**, Blakemore AIF, Duff GW (1992)
-J- "Single base polymorphism in the human TNF alpha gene detectable by Ncol
restriction of PCR product" **HUMAN MOL. GENETICS**, 1, 353.
- 25- Bailly, S, **di Giovine, FS**, Duff GW (1993)

- J- "Polymorphic tandem repeat region in Interleukin 1 alpha intron 6"
HUM. GENETICS., 91, 85.
- 26 Bailly, S, **di Giovine, FS**, Blakemore, AIF, Duff GW (1993). "Genetic polymorphism of -J- human Interleukin 1 alpha due to a variable number of intronic repeats"
EUR. J. IMMUNOL. , 23, 1240-1245.
- 27 Wilson A G, de Vries,N., Pociot F, **di Giovine F S**, Van de Putte L., Duff G W (1993)
-J- "An allelic polymorphism within the human necrosis factor alphas promoter region is strongly associated with HLA A1, B8, and Dr3 alleles" **J. EXP. MED** , 177, 557.
- 28 Wilson A G , Gordon C, **di Giovine F S**, de Vries N, Emery P., and G W Duff. (1994)
-J- "A genetic association between Systemic Lupus Erithematosus and Tumour Necrosis Factor Alpha" **EUR. J. IMMUNOL.** , 24, 191-195.
- 29 **di Giovine, FS**, Bailly S., Bootman J., Almond N., Duff, GW (1994)
-P- "Absence of lentiviral and HTLV sequences in patients with rheumatoid arthritis"
ARTHRITIS RHEUM., 37, 349-358.
- 30 Mansfield, J, Holden, H., Tarlow, J., **di Giovine, FS**, McDowell, TL, Wilson, AG, Duff GW -J- (1994). "Novel genetic association between Ulcerative Colitis and anti-inflammatory cytokine IL-1 receptor antagonist" **GASTROENTEROLOGY** , 106, 637-642.
- 31 Rooney,M., David, J., Symons, J., **di Giovine, FS**, Varsani, H., Woo P (1995)
-J- "Inflammatory cytokine responses in juvenile chronic arthritis"
BR. J. RHEUMATOL. , 34, 454-460.
- 32 Wilson, AG, **di Giovine, FS**, Duff GW (1995)
-J- "Genetics of tumor necrosis factor alpha in autoimmune, infectious and neoplastic diseases"
J.INFLAMMATION , 45, 1-12.
- 33 Tagariello, G., **di Giovine, FS**. (1996) "Cytokines in the pathogenesis of haemophilia arthritis" **THROMB. HAEM.** , 75, 979-980. (LETTER)
- 34 Demeter, J., Messer G, Ramish S, Mee JB, **di Giovine FS**, Herrmann F., Schmid M, Porzsolt F. (1996) " Polymorphism within the second intron of the IL-1 RN gene in patients with haematological malignancies" **CYTOKINES MOL. THERAPY** , 2, 239-242.
- 35 Korman, KS, Crane, A., Wang, HY., **di Giovine, FS**,Pirk, FW, Wilson, TG, Higginbottom, F, -J- Newman, MG, Duff GW (1997) "The IL-1 genotype as a severity factor in periodontal disease" **J. CLIN. PERIODONTOL** 24:72-77.
- 36 - Cox, A., Camp, NJ, Nicklin, MJH, **di Giovine, FS**, Duff, GW, (1998)
-J- "An analysis of linkage disequilibrium in the Interleukin-1 gene cluster, using a novel grouping method for multiallelic markers" **AM. J. HUM. GENET.** 62: 1180-1188.
- 37- Stephens, JC, Reich D.E., Goldstein D B, ..., **di Giovine, FS**, ..., O'Brien SJ, Dean M - (multiple authors) (1998) "Dating the Origin of the *CCR5-Δ32* AIDS resistance Gene by the Coalescence of Haplotypes"
AM. J. HUM. GENET. 62: 1507-1515
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-J- "Genetic Variations In Cytokine Expression: A Risk Factor For Severity Of Adult Periodontitis" **ANNALS PERIODONTOL**, 3: 327-338.
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6.4 REFERRED ABSTRACTS

A total of 126 research abstracts , peer reviewed and published.

7- Research interests

Most of my research in the past five years have been in the area of cytokine genotype correlation with phenotypes, both at the level of cellular biology (i.e. mechanisms of differential function) and at the clinical outcome level, where I have collaborated and have grant funding with a number of colleagues. The final aim of this effort is to understand the underlying contribution of cytokine genetics to inflammatory diseases. Identification of novel disease mechanisms or susceptibility factors may be useful to the development of new therapeutic approaches and patient targeting.

8- Internal Referees

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Molecular Biology and Biotechnology,
Firth Court, Western Bank, University of Sheffield (UK)
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ATTACHMENT B

Application No.: 09/247,874

Inventor: Duff, et al.

Examiner: R. Schnizer

The logo for ABE PRISM, featuring the word "ABE" above "PRISM" with a stylized pencil graphic.

Model 373A
Version 3.3

Version 1.2

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